Neuroscience and Biobehavioral Reviews 51 (2015) 100–107

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Sleep, arousal, and circadian rhythms in adults with obsessive–compulsive disorder: A meta-analysis

Jacob A. Nota[a,*], Katherine M. Sharkey[b], Meredith E. Coles[a]

[a] Department of Psychology, Binghamton University, PO Box 6000, Binghamton, NY 13902-6000, United States
[b] Departments of Medicine and Psychiatry & Human Behavior, Rhode Island Hospital/Brown University, 300 Duncan Drive, Providence, RI 02906, United States

ARTICLE INFO

Article history:
Received 8 August 2014
Received in revised form 18 October 2014
Accepted 5 January 2015
Available online 18 January 2015

Keywords:
Sleep
Arousal
Circadian rhythm
Bedtime
Obsessive–compulsive disorder

ABSTRACT

Findings of this meta-analysis show that obsessive–compulsive disorder (OCD) is related to disruptions in both the duration and timing of sleep. PsycINFO and Google Scholar database searches identified 12 relevant studies that compared measures of sleep in individuals with OCD to those of either a healthy control group or published norms. Sleep measures included sleep onset latency, sleep duration, awakening after sleep onset, percentage of rapid eye movement (REM) sleep, percentage of slow wave sleep, and prevalence of delayed sleep phase disorder (DSPD). Individual effect sizes were pooled using a random effects model. Sleep duration was found to be shorter, and the prevalence of DSPD higher, in individuals with OCD compared to controls. Further, excluding samples with comorbid depression did not meaningfully reduce the magnitude of these effects (although the results were no longer statistically significant) and medication use by participants is unlikely to have systematically altered sleep timing. Overall, available data suggest that sleep disruption is associated with OCD but further research on both sleep duration and sleep timing in individuals with OCD is needed.

© 2015 Elsevier Ltd. All rights reserved.

Contents

* Corresponding author. Tel.: +1 607 777 5006.
E-mail address: jnota1@binghamton.edu (J.A. Nota).

http://dx.doi.org/10.1016/j.neubiorev.2015.01.002
0149-7634/© 2015 Elsevier Ltd. All rights reserved.

1. Background

A growing literature suggests that biological regulatory systems (i.e., sleep/wakefulness, arousal, circadian rhythms) may influence psychiatric symptoms directly and/or in combination with the environment and behavior (Harvey, 2011; Wulff et al., 2010). Indeed, these systems are increasingly recognized as an avenue for furthering our understanding of mechanisms and enhancing interventions for psychiatric disorders [e.g., bipolar disorder (Jones, 2001) schizophrenia (Chouinard et al., 2004) and autism (Glickman, 2010)]. While, it is acknowledged that these systems are worthy of further study, research for some disorders, including obsessive–compulsive disorder (OCD), has been limited by a lack of comprehensive quantitative information about these systems and a framework with which to understand this information.

Differences in sleep behavior (i.e., reduced total sleep time, increased awakenings after sleep onset, extended sleep onset latency) have been documented in individuals with OCD compared to healthy individuals (Arriaga et al., 1995; Gaillard et al., 1984; Insel et al., 1982; Kluge et al., 2007; Ramsawh et al., 2009; Robinson et al., 1998; Voderholzer et al., 2007; Walsleben et al., 1990; Hohagen et al., 1994). Differences in the architecture of sleep [i.e., decreased latency to the onset of rapid eye movement (REM) sleep and increased density of REM sleep] have also been associated with OCD (Gaillard et al., 1984; Walsleben et al., 1990). A pattern of delayed sleep onset and offset in relation to desired bed and wake times resulting in significant distress and/or interference, known as delayed sleep phase disorder (DSPD, American Academy, 2001; Weitzman et al., 1981), also appears to be prevalent in individuals with severe OCD (Bobdey et al., 2002; Mukhopadhyay et al., 2008; Turner et al., 2007). Some of these findings appear to be relatively unique to individuals with OCD (e.g., increased DSPD prevalence); yet, others are common to psychiatric disorders (Benca et al., 1992) and the possible influence of comorbid depression can also not be ruled out (Paterson et al., 2013). Thus far, tools for aggregating and evaluating quantitative findings across studies (Lipsey and Wilson, 2001) have not been applied to the existing literature.

Utilizing a framework that accommodates the multiple regulatory processes that influence sleep may also facilitate identification of which processes are associated with psychopathology, including OCD. As part of the National Institute of Mental Health Research Domain Criteria (RDoC) initiative (National Institute, 2013), an expert panel recently delineated three primary constructs related to arousal and regulatory systems: (1) arousal: an organism's fluctuating sensitivity to stimuli; (2) circadian rhythms: endogenous oscillations that coordinate the timing between internal physiology and external behavior; and (3) sleep and wakefulness: distinct states of functional organization of the brain that are reflected in behavior as well as electroencephalograph recordings of brain activity. Each of these processes appears to have shared and unique physiological mediators (Schwartz and Roth, 2008); therefore, it is desirable to differentiate these mechanisms in order to inform hypotheses about the relation between sleep patterns and OCD.

Importantly, these regulatory system constructs are variously reflected in observable measures of sleep. For example, the duration of sleep during a given night is influenced by a homeostatic drive, a characteristic of sleep/wake regulation where increasing time awake leads to greater sleep pressure and thus a greater amount of sleep time is needed to neutralize the pressure to sleep (Borbely and Achermann, 2005). Arousal can also influence the duration of sleep. For instance, heightened arousal associated with states of anxiety has been show to increase sleep onset latency and decrease reports of restful sleep (Haynes et al., 1981; Tang and Harvey, 2004). The phase of circadian rhythms during sleep bouts also modulates sleep propensity and thus influences sleep duration (Dijk and Czeisler, 1994; Dijk and Franken, 2005). Therefore, sleep duration can be understood to reflect all three constructs: sleep/wakefulness, arousal, and circadian rhythmicity. Alternatively, the amount of rapid eye movement (REM) sleep one experiences during a given period is understood to be a product of both homeostatic sleep drive and circadian phase (Dijk and Czeisler, 1995), but is not believed to be influenced by arousal. Based on this principle, it is thus possible to construct a framework for inferring the involvement of arousal and regulatory systems based on observed differences in sleep behavior. This may inform more focused studies in the future.

2. The current study

Our purpose in the current review is to examine quantitative information about the sleep of individuals with OCD in comparison to healthy individuals. We chose to examine sleep outcomes that tap various sleep-related constructs in order to cast a wide net for detecting possible differences between individuals with OCD and healthy controls. By acknowledging that these markers of sleep are multiply determined, we will use these findings to suggest possible disruptions in sleep-related mechanisms. Further, informed by hypotheses derived from previous reviews of this literature (Paterson et al., 2013), we will also attempt to address the whether sleep disruptions exist in individuals with OCD who do not have comorbid depression.

3. Method

3.1. Study selection

We included studies that compare measures of sleep in individuals with OCD to those of either a healthy control group or published norms for healthy individuals. In order to provide a comprehensive review of the literature, we did not impose a limit on the publication date or country (provided the report was written in English). Sleep could be measured by self-report questionnaire, third-party observation, actigraphy, or polysomnography. We did not limit the time course of sleep variable measurement (e.g., self-report over the past month or polysomnography recordings from two nights in a sleep lab). Our only exclusion criteria were studies that: (1) reported data that overlapped with the data from other included studies; (2) did not include a healthy control group or compare individuals with OCD to norms for healthy individuals; (3) manipulated sleep by administration of drugs or sleep deprivation; (4) reported insufficient information to compute an effect size; and (5) studies that included children. We chose to exclude studies of children because of well-described changes in sleep mechanisms across development (Crowley et al., 2007).

3.2. Search strategy

We conducted database searches of PsycInfo and Google Scholar during the period from February 2013 to February 2014. Search terms included "obsessive–compulsive", "OCD", "sleep", "arousal", and "circadian rhythms". We examined all published materials available. We also reviewed article reference sections for possibly relevant study titles. The first author examined titles for all returned articles for possible relevance. Abstracts for any papers with relevant titles were also examined. At this point, if the article was still deemed to be relevant, the full text was read and coded for study characteristics and relevant outcomes. Decisions about which studies to include were made by the first author (JN).

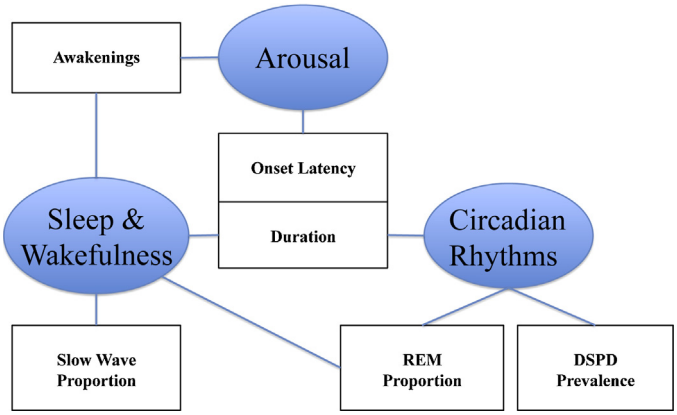

Fig. 1. Conceptual model relating observed sleep outcomes and theoretical arousal and regulatory systems constructs. Observed sleep outcomes are represented as boxes. Theoretical arousal and regulatory systems constructs are represented as blue ovals.

3.3. Sleep measures: Definitions and assignment to bioregulatory construct categories

Given the varying methodologies utilized by the included studies, we chose to examine measures of sleep that would maximize both the number of studies that contribute data and coverage of the bioregulatory constructs of interest. Thus, we identified three constructs: arousal, homeostatic sleep processes, and circadian rhythms and assigned sleep measures to one or more of these constructs. These constructs were derived mainly from the RDoC (National Institute, 2013) arousal and regulatory systems domains.

Based on the suggestions from the RDoC expert panel (National Institute, 2013) and our own research, we have constructed a framework to relate observable measures of sleep to latent regulatory constructs (see Fig. 1). We utilized this framework to infer the probability of RDoC construct involvement in the relation between OCD and sleep by examining the relative strengths of the effects related to each construct.

The six sleep measures examined were determined a priori and include sleep onset latency, sleep duration, awakening after sleep onset, proportion of rapid eye movement (REM) sleep, proportion of slow wave sleep, and prevalence of delayed sleep phase disorder. We operationalized our outcomes in a manner that could be applied consistently across the various methodologies used in the included studies. In studies that utilized polysomnography, the sleep onset latency was defined as the first presence of stage N2 sleep. Sleep onset latency was defined as the reported time needed for an individual to fall asleep after lying down in bed. Sleep duration was operationalized as the total time spent during a given night (from sleep onset until ultimate awakening). Wake after sleep onset was operationalized as the total time spent awake during sleep period time (lights out to lights on) or alternatively the percentage of sleep period time spent awake. The percent of REM sleep was operationalized as the percent of the total sleep spent in REM. Similarly, the percent of slow wave sleep was operationalized as the percent of the total sleep spent in slow wave (stages N3 and/or N4) sleep. For studies that utilized self-report measures; sleep onset latency, sleep duration, and time spent awake after sleep onset were operationalized as reports of habitual duration of each measure, respectively.

The final sleep measure was different from the other outcomes, as it was not a direct measure of a sleep variable, but instead examined the prevalence of a circadian rhythm sleep disorder, DSPD in the study sample. In the studies included in the current analysis, DSPD was operationalized as habitual delayed bed and wake times as determined by either third party observation of individuals during inpatient hospital stays or by examining the proportion of individuals who exceeded the 90th percentile in their reports of habitual bedtimes on the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). Unfortunately, there were no studies that utilized actigraphy in defining DSPD. This method is considered a "gold standard" measure (American Academy, 2014) and would have been included if available.

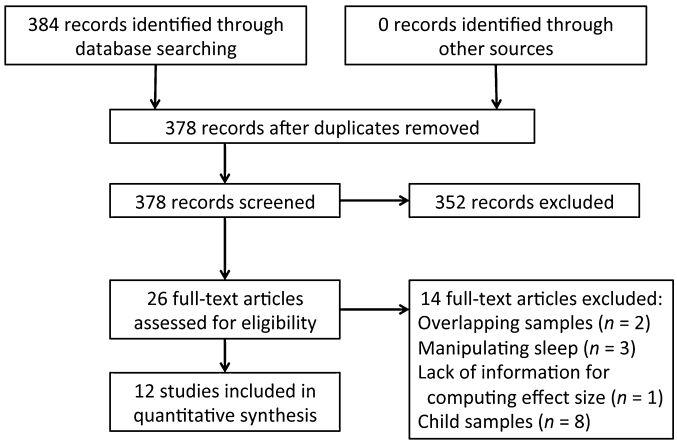

Fig. 2. Study selection process.

3.4. Statistical analyses

We computed standardized differences in means between the OCD and healthy groups using Microsoft Excel. Hedge's *g*, and standard errors were computed using means and standard deviations when available; in the remaining cases effect sizes were computed using reported statistics (e.g., *F*, *t*, χ^2). Individual effect sizes were pooled using a random effects model to determine mean effect sizes across studies and 95% confidence intervals. This choice accommodates for the methodological heterogeneity of the selected studies (Lipsey and Wilson, 2001; Borenstein et al., 2009). Herein, $.20 \leq g < .50$ was considered a small effect, $.50 \leq g < .80$ was considered a medium effect, and $g \geq .80$ was considered a large effect (Cohen, 1988). We systematically assessed the heterogeneity of the effect sizes included in each mean effect size using *Q* and I^2 (Borenstein et al., 2009; Neyeloff et al., 2012). We interpreted an $I^2 \geq 25\%$ as low, $I^2 \geq 50\%$ as moderate, and $I^2 \geq 75\%$ high in heterogeneity (Higgins et al., 2003). It should be noted that *Q* and I^2 have limited power to detect statistically significant heterogeneity in effect sizes when there are few studies included in a meta-analysis, as in the current study (Huedo-Medina et al., 2006). Therefore, we examined these statistics primarily for descriptive purposes and did not make analysis choices based upon their statistical significance. We planned a priori to compute mean effect size estimates using a random effects model for the subset of studies that excluded individuals with comorbid depression from their OCD group because of the theoretical importance of this relation. We created forest plots to visually examine the mean effect sizes and constructed funnel plots for each sleep outcome to examine the possibility of bias across studies.

4. Results

4.1. Search results

PsycInfo and Google Scholar searches yielded 340 publications and 44 publications, respectively. After assessment of the publications and application of exclusion criteria, 12 articles were retained for the review (see Fig. 2). The sample and methodological characteristics and effect sizes of these 12 studies are described in

Table 1
Study characteristics and effect sizes.

Study	OC (*n*)	HC (*n*)	Method	MDD	Duration *g* (SE)	SOL *g* (SE)	Awake *g* (SE)	Slow *g* (SE)	REM *g* (SE)	DSPD *g* (SE)
Insel et al.	14	14	PSG	Y	−1.24 (.41)	.19 (.38)	.92 (.40)	−.95 (.40)	.45 (.38)	–
Hohagen et al.	22	22	PSG	Y	−.08 (.30)	.10 (.30)	.60 (.31)	−.13 (.30)	.05 (.30)	–
Gaillard et al.	5	15	PSG	N	−.26 (.52)	−.08 (.52)	1.07 (.54)	−1.59 (.57)	.82 (.53)	–
Ariaga et al.	16	28	SR	N	−.35 (.32)	1.01 (.33)	.44 (.32)	–	–	–
Robinson et al.	13	13	PSG	N	−.12 (.39)	−.69 (.40)	.05 (.39)	.10 (.39)	.28 (.39)	–
Walsleben et al.	6	10	PSG	N	−2.54 (.68)	.28 (.52)	–	3.09 (.75)	−2.06 (.63)	–
Ramsawh et al.[b]	26	4137[a]	SR	Y	−.79 (.20)	1.19 (.20)	3.10 (.20)	–	–	–
Voderholzer et al.	62	62	PSG	Y	−.76 (.19)	.17 (.18)	.63 (.18)	−.04 (.18)	.06 (.18)	–
Kluge et al.	10	10	PSG	N	−.64 (.46)	−.36 (.45)	−.07 (.45)	−.36 (.45)	.63 (.46)	–
Bobdey et al.[b]	12	57	SR	N	−.27 (.32)	.47 (.32)	–	–	–	.69 (.32)
Turner et al.[b]	28	10,000[a]	3PO	N	–	–	–	–	–	3.34 (.18)
Mukhapdhyay et al.[b]	187	10,000[a]	3PO	Y	–	–	–	–	–	2.66 (.08)

Note: PSG = polysomnography; SR = self report; 3PO = third party observation; duration = sleep duration; SOL = sleep onset latency; awake = awakenings; slow = slow wave proportion; REM = REM proportion; DSPD = DSPD prevalence. All effect sizes reported as Hedge's *g*.

[a] Comparison based on published norms for healthy group.

[b] Sample included individuals taking psychotropic medication.

Table 1. Self-report measures of sleep utilized in the reviewed studies included the PSQI (Buysse et al., 1989) and the Spiegel Questionnaire (Spiegel, 1981). Third-party observations were conducted in inpatient hospital settings. Polysomnography studies all included one night of habituation to the laboratory setting, followed by one to four nights of polysomnographic recordings. Eight of the 12 studies included in this meta-analysis excluded individuals taking psychotropic medication at the time of the study. Individuals in the OCD group had been clear of psychotropic medication for a minimum of one week (mode duration = two weeks) with extended minimums (4–6 weeks) in place for medications including fluoxetine, MAO inhibitors, neuroleptics, and benzodiazepines. In the four studies that allowed medications (Ramsawh et al., 2009; Bobdey et al., 2002; Mukhopadhyay et al., 2008; Turner et al., 2007), only three reported information about these medications (Bobdey et al., 2002; Mukhopadhyay et al., 2008; Turner et al., 2007). Among those, the use of hypnotics was very rare ($n = 18$ out of $n = 227$ in these studies; 7.9%); however, use of SSRIs was common ($n = 149$; 65.6%). All individuals in the OCD groups were diagnosed using criteria from the Diagnostic and Statistical Manual (DSM, American Psychiatric Association, 1980, 1987, 1994, 2000) or the International Classification of Diseases (ICD, World Health, 1979). Across all studies, data from a total of 404 patients and 231 healthy controls (not including comparisons to published norms) were included.

4.2. Mean effect size estimates

Mean random effects effect size estimates and 95% confidence intervals are presented in Fig. 3a. Two effect size estimates were found to be significant. First, sleep duration was shorter in individuals with OCD compared to healthy individuals. The magnitude of this difference is in the medium range ($g = -.60$; 95% CI [−.90, −.31]); heterogeneity among studies was low and not statistically significant ($Q = 11.81$, $p = .22$; $I^2 = 23.81\%$). Second, the prevalence of DSPD in the individuals with OCD was also significantly greater than healthy individuals. The magnitude of this difference is large ($g = 2.28$; 95% CI [1.28, 3.27]); heterogeneity among studies was moderate but not statistically significant ($Q = 4.72$, $p = .09$; $I^2 = 57.61\%$).

Estimates of the remaining measures were not reliably different from zero but differences between the groups were notable. Individuals with OCD spent more time awake after sleep onset compared to healthy individuals. The evidence suggests that the magnitude of this difference is large ($g = .86$; 95% CI [−.04, 1.76]). Heterogeneity among studies was low and not statistically significant ($Q = 4.24$, $p = .75$; $I^2 = 0.00\%$). The difference in sleep onset latency for individuals with OCD and healthy controls was small, but still notable ($g = .28$; 95% CI [−.10, .67]). Heterogeneity among studies was also low and not statistically significant ($Q = 7.80$, $p = .55$; $I^2 = 0.00\%$). Finally, the proportion of sleep spent in slow wave and REM sleep stages did not statistically significantly differ between the individuals with OCD and the healthy individuals ($g = -.11$; 95% CI [−.73, .52] and $g = .12$; 95% CI [−.33, .56], respectively); however, heterogeneity among studies was moderate for both measures and statistically significant for the proportion of slow wave sleep ($Q = 13.19$, $p = .04$; $I^2 = 54.51\%$ and $Q = 9.83$, $p = .13$; $I^2 = 38.98\%$, respectively).

In order to confirm that medication use did not bias the mean effect size estimates, we replicated the analyses of mean random-effects effect sizes using the subset of studies that excluded individuals currently taking psychotropic medication. This removed four studies (see Table 1). With regard to the previously significant effects: sleep duration remained reliably shorter in individuals with OCD compared to healthy individuals and was similar in magnitude to the overall mean effect size ($g = -.62$; 95% CI [−1.02, −.23]); however, it was impossible to calculate a comparison for the prevalence of DSPD since all of the studies that examined the prevalence of DSPD included individuals taking psychotropic medications. Individuals with OCD who were free from psychotropic medications also spent more time awake after sleep onset compared to healthy individuals. The magnitude of this effect was more modest than the overall mean effect size, but was now statistically significant ($g = .55$; 95% CI [.33, .77]). The difference in sleep onset latency for individuals with OCD and healthy controls was smaller than the overall mean effect size ($g = .12$; 95% CI [−.21, .45]). Finally, the proportion of sleep spent in slow wave and REM sleep stages was not affected as all of the studies that contributed to the overall mean effect size estimate excluded individuals using psychotropic medication.

4.3. Comorbid depression

Mean random-effects effect size estimates and 95% confidence intervals for studies that compared individuals with OCD without comorbid depression to healthy controls are presented in Fig. 3b. When examining this subset of studies, the magnitude of the two previously significant outcomes (sleep duration and DSPD prevalence) reduced only slightly. The sleep duration effect remained in the medium range ($g = .53$) and remained significantly different from zero (95% CI [−1.02, −.04]). The prevalence of DSPD effect was also relatively similar ($g = 2.03$), although the reliability of this difference decreased to the point of non-significance (95% CI [−.56, 4.62]).

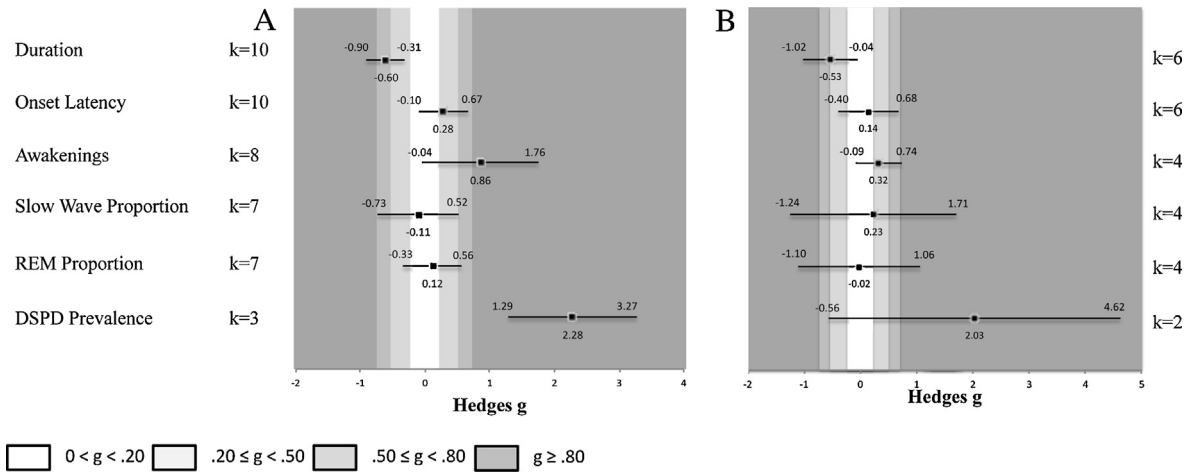

Fig. 3. Mean Hedge's *g* and 95% confidence intervals for all sleep outcomes. (A) All OCD compared to healthy control. (B) OCD without comorbid depression compared to healthy control. Gradations indicate small ($g \geq .20$), medium ($g \geq .50$), and large ($g \geq .80$) effect sizes. Note that REM = rapid eye movement; DSPD = delayed sleep phase disorder; and k = number of effect sizes included in random effects estimate.

The other previously notable effects were changed by at least an order of magnitude when examining the subset of studies that compared individuals with OCD without comorbid depression to healthy controls (i.e., the pure OCD group). Both the sleep onset latency ($g = .14$) and the time spent awake after sleep onset ($g = .32$) effects became smaller compared to the overall mean effect size estimates and neither was reliably different from zero (95% CI [−.40, .68] and [−.09, .74], respectively). The pure OCD group spent a greater proportion of sleep in slow wave stages ($g = .23$; 95% CI [−1.24, 1.70]) compared to the healthy control group, a small effect not present in the full sample. Finally, similar to the complete OCD group, the pure OCD group spent a similar proportion of sleep in REM stages ($g = -.02$) compared to the healthy control group.

4.4. Publication bias

We created funnel plots for each sleep outcome to examine the possibility of bias across studies [see Fig. 4; (Egger et al., 1997)]. Funnel plots were generally not suggestive of publication bias. Asymmetry of studies in the lower left quadrant of the funnel, compared to the lower right suggests that the mean effect sizes may provide upwardly-biased estimates of the differences between individuals with OCD and healthy controls on measures of sleep duration and proportion of sleep spent in REM (Borenstein et al., 2009); however, the small sample sizes of the included studies meant that the overall precision was low.

5. Discussion

Findings of this analysis suggest that the sleep of individuals with OCD differs from healthy controls. Further, this difference cannot be attributed to psychotropic medication use or the presence of comorbid depression. Sleep disruption compared to healthy control groups has previously been documented in individuals with mood disorders, anxiety disorders, and schizophrenia (Wulff et al., 2010; Benca et al., 1992). There is increasing evidence that this relation has implications for individuals' overall functioning (Cajochen et al., 2004; Gangwisch et al., 2006; Kajtna et al., 2011; van der Helm and Walker, 2009; Wright et al., 2006) as well as their psychiatric symptoms (Harvey et al., 2011; Perlis et al., 1997; Ford and Kamerow, 1989; Breslau et al., 1996). To continue advancing our understanding of this relation and how it can be addressed empirically it is also important that we consider sleep in as sophisticated a fashion as we do the waking behavior we are seeking to relate to sleep.

Examining the findings of this review in the context of the proposed framework (see Fig. 1) suggests that certain regulatory system constructs may be more likely to account for observed differences between individuals with OCD and healthy controls. Overall, the largest differences were detected in measures related to the circadian rhythms construct. Notably, a significant and large group difference was found in the prevalence of DSPD in individuals with and without OCD. Studies in unselected samples have found that delayed bedtimes are associated with increased OC symptoms (Coles et al., 2012). Samples recruited for DSPD also have heightened rates of OCD diagnoses (Abe et al., 2011; Schubert and Coles, 2013). Further, there is initial evidence that treatments aimed at addressing delayed bedtimes (Coles and Sharkey, 2011) and subjective sleep disruption (Abe et al., 2012) may reduce OC symptoms. Given that DSPD is maintained by a shift in the phase of biological circadian rhythms (Weitzman et al., 1981), further research on the relation between DSPD and OCD may help to yield novel clues as to the pathophysiology of OCD.

Beyond DSPD prevalence, there were medium to large effects that implicated the arousal and sleep and wakefulness constructs. We found that individuals with OCD demonstrated reliably shorter duration of sleep compared to controls. As this is one of the most general sleep measures, it can be affected by any of the regulatory system constructs. Sleep onset latency, another measure of sleep affected by all three regulatory system constructs, trended toward a small mean increase in sleep onset latency for individuals with OCD. Sleep onset latency increases have been associated with other perseverative intrusive thought phenomena (e.g., rumination, worry) (Thomsen et al., 2003). This may suggest that processes related to the maintenance of such phenomena (i.e., increased attention to thoughts, poor cognitive control, deficits in response inhibition) are related to difficulty initiating sleep. Alternatively, longer sleep onset latency coupled with shorter sleep durations may exacerbate worry, rumination, and obsessions by decreasing the ability to inhibit attention to thoughts and cognitive or behavioral responses to thoughts. It is interesting to note that, while sleep onset latency has been associated with a number of disorders with perseverative thought processes, time spent awake during the night is less frequently associated with these other disorders. However, nighttime awakenings are sometimes associated with other types of anxiety symptoms; for example, nocturnal panic attacks. The significant moderate increase in time spent awake after sleep onset among

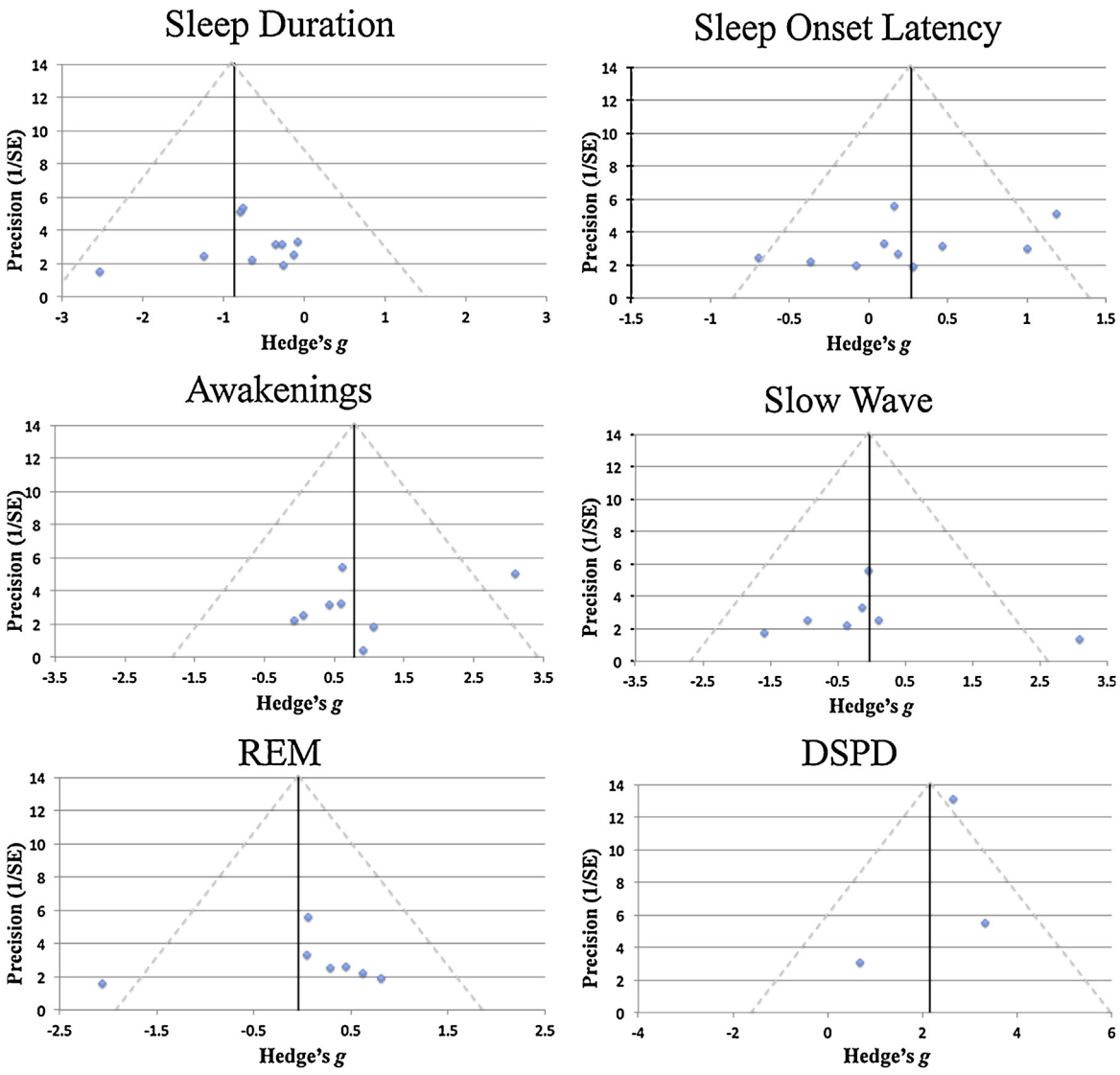

Fig. 4. Funnel plots. The distribution of effect sizes is displayed in relation to the mean effect size and precision of the estimates. A plot with a skewed distribution may suggest bias in the mean effect size estimate. Note that REM = rapid eye movement and DSPD = delayed sleep phase disorder.

individuals with OCD (without any psychotropic medication use) in the current study suggests that this measure of sleep may capture an aspect of sleep disruption that is shared by individuals with OCD and forms of anxiety other than worry and rumination. Diurnal rhythms of OC symptoms measured in a clinical population (Nota et al., 2014) have also been found to be more similar to panic anxiety symptoms (Kenardy et al., 1992) rather than to other perseverative thought processes (Takano and Tanno, 2011). Given that time spent awake after sleep onset is related to the arousal construct, this may suggest that increased arousal plays a role in the experience of individuals with OCD that is unique from the more extensively studied populations of depressed and worried individuals.

When excluding studies with individuals with comorbid depression (see Fig. 3b) we found that effect sizes were generally similar to the full sample of studies; time spent awake after sleep onset was the only outcome to change by an order of magnitude. This is perhaps surprising, considering the literature documenting a relation between mood disorders and sleep disturbance (for review see, Tsuno et al., 2005). When considered in the context of the proposed framework (see Fig. 1), it is notable that the awakenings after sleep onset effect size (related to sleep/wakefulness and arousal constructs) became weaker by an order of magnitude, while the prevalence of DSPD (related to circadian rhythms construct) remained similar in magnitude. This seems to suggest the possibility that the relation between OCD diagnosis and DSPD diagnosis may be the strongest among those examined herein. Another interesting finding was the statistically significant heterogeneity observed in the slow wave sleep effect sizes and the shift in the direction of the effects for the proportion of slow wave and REM sleep when individuals with comorbid depression were excluded. Specifically, when those with comorbid depression were included, the OCD group demonstrated a slightly higher proportion of REM and lower proportion of slow wave sleep compared to healthy controls. This is consistent with other studies showing that increased REM is linked with psychopathology (van der Helm and Walker, 2012). Alternatively, when those with comorbid depression were excluded, the OCD group demonstrated a slightly higher proportion of slow wave and lower REM sleep compared to healthy individuals. This pattern has been previously found in individuals who have experienced sleep deprivation (Borbely and Achermann, 2005). Sleep deprivation has been shown to cause difficulty sustaining attention, shifting attention, and regulating emotion (Cajochen et al., 2004; van der Helm and Walker, 2009; Norton, 1970) similar to impairments observed in

patients with OCD. Further study in individuals with OCD and without comorbid depression is needed to clarify these findings.

5.1. Limitations

Overall, this review suggests there are meaningful differences in the sleep of individuals with OCD compared to healthy individuals, and has identified potential targets for future study. However, the controlled correlational design of the studies included in this meta-analysis does not account for the temporal relation between sleep disturbance and OCD, therefore it may be the case that the presence of OCD leads to disruptions of sleep or vice versa. An unexamined third variable could also account for the observed differences between the groups: for example, the level of psychological distress. An additional limitation is that the studies examining DSPD included individuals taking psychotropic medications, primarily SSRIs, thereby confounding potential sleep problems with consequences of the medication. However, there is no reason to posit that SSRIs would systematically delay circadian rhythms, contributing to the findings regarding DSPD herein. Indeed, increased serotonin levels have a differential impact on circadian rhythms depending on the time of dosing. Specifically, taking the medication in the morning to midday would *delay* circadian rhythms while midday to evening dosing would *advance* circadian rhythms) (Ciarleglio et al., 2011; Ohdo, 2007; Oral et al., 2011). This review also only examined published studies, increasing the risk that our estimates are biased toward larger differences between the groups. Examination of the funnel plots suggests that our estimates are relatively representative of the studies included. However, the addition of future studies, controlling for psychotropic medication use, will allow for increased confidence in effect size estimates.

5.2. Conclusion

Individuals with OCD have demonstrated differences in their sleep behavior compared to healthy controls. It remains to be determined what the impact of these differences is for the functioning of individuals with OCD; however, studies suggest that even seemingly small differences in sleep can, over time, have important consequences (Gangwisch et al., 2006; Cappuccio et al., 2008). These differences appear to be attributable to disruptions in circadian rhythms, though more work is needed to clarify this association. Continuing to study these systems in individuals with OCD may prove to be a novel approach to understanding the pathophysiology and maintenance of OC symptoms. We hope the information gleaned from this review will be used to inform future studies and advance our understanding of OCD.

Financial disclosures

KS currently receives funding from the National Institute of Health (K23 MH086689).

Acknowledgments

JN had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. JN conducted the database search, evaluated the returned sources, compiled individual effect sizes, computed mean effect sizes using the random effects model, and was the primary author of the manuscript. KS contributed to the construction of the framework for interpreting observable measures and the organization of the manuscript. MC contributed to the statistical analysis, design of manuscript figures, and the preparation of the manuscript.

References [1]

Abe, T., Inoue, Y., Komada, Y., et al., 2011. Relation between morningness–eveningness score and depressive symptoms among patients with delayed sleep phase syndrome. Sleep Med. 12 (7), 680–684.

Abe, Y., Nishimura, G., Endo, T., 2012. Early sleep psychiatric intervention for acute insomnia: implications from a case of obsessive–compulsive disorder. J. Clin. Sleep Med. 8 (2), 191–193, http://dx.doi.org/10.5664/jcsm.1778; 10.5664/jcsm.1778.

American Academy of Sleep Medicine, 2001. International Classification of Sleep Disorders. American Academy of Sleep Medicine, Westchester, IL.

American Academy of Sleep Medicine, 2014. International Classification of Sleep Disorders, third ed. American Academy of Sleep Medicine, Darien, IL.

American Psychiatric Association, 1980. Diagnostic and Statistical Manual of Mental Disorders, third ed. Author, Washington, DC.

American Psychiatric Association, 1987. Diagnostic and Statistical Manual of Mental Disorders, third. rev. ed. Author, Washington, D.C.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV, fourth ed. Author, Washington, D.C.

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR, 4th, text revised ed. Author, Washington, D.C.

*Arriaga, F., Lara, E., Matos-Pires, A., Cavaglia, F., Bastos, L., 1995. Diagnostic relevance of sleep complaints in anxiety and mood disorders. Eur. Psychiatry 10 (8), 386–390.

Benca, R.M., Obermeyer, W.H., Thisted, R.A., Gillin, J.C., 1992. Sleep and psychiatric disorders. A meta-analysis. Arch. Gen. Psychiatry 49 (8), 651–668.

*Bobdey, M., Fineberg, N., Gale, T., Patel, A., Davies, H., 2002. Reported sleep patterns in obsessive compulsive disorder (OCD). Int. J. Psychiatry Clin. Pract. 6 (1), 15–21.

Borbely, A.A., Achermann, P., 2005. Sleep homeostasis and models of sleep regulation. In: Principles and Practice of Sleep Medicine. Elsevier Saunders, Philadelphia, PA, pp. 405–417.

Borenstein, M., Hedges, L., Higgins, J.P., Rothstein, H.R., 2009. Introduction to Meta-Analysis. John Wiley & Sons, West Sussex, UK.

Breslau, N., Roth, T., Rosenthal, L., Andreski, P., 1996. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. Biol. Psychiatry 39 (6), 411–418.

Buysse, D.J., Reynolds III, C.F., Monk, T.H., Berman, S.R., Kupfer, D.J., 1989. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 28 (2), 193–213.

Cajochen, C., Blatter, K., Wallach, D., 2004. Circadian and sleep-wake dependent impact on neurobehavioral function. Psychol. Belg. 44 (1), 59–80.

Cappuccio, F.P., Taggart, F.M., Kandala, N.B., et al., 2008. Meta-analysis of short sleep duration and obesity in children and adults. Sleep 31 (5), 619–626.

Chouinard, S., Poulin, J., Stip, E., Godbout, R., 2004. Sleep in untreated patients with schizophrenia: a meta-analysis. Schizophr. Bull. 30 (4), 957–967.

Ciarleglio, C., Resuehr, H., McMahon, D., 2011. Interactions of the serotonin and circadian systems: nature and nurture in rhythms and blues. Neuroscience 197, 8–16.

Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences, second ed. Lawrence-Erlbaum Associates, New Jersey.

Coles, M.E., Sharkey, K.M., 2011. Compulsion or chronobiology? A case of severe obsessive–compulsive disorder treated with cognitive-behavioral therapy augmented with chronotherapy. J. Clin. Sleep Med. 7 (3), 307–309.

Coles, M.E., Schubert, J.R., Sharkey, K.M., 2012. Delayed bedtimes and obsessive–compulsive symptoms. Behav. Sleep Med. 10 (4), 258–265.

Crowley, S.J., Acebo, C., Carskadon, M.A., 2007. Sleep, circadian rhythms, and delayed phase in adolescence. Sleep Med. 8 (6), 602–612.

Dijk, D., Czeisler, C.A., 1994. Paradoxical timing of the circadian rhythm of sleep propensity serves to consolidate sleep and wakefulness in humans. Neurosci. Lett. 166 (1), 63–68.

Dijk, D., Czeisler, C.A., 1995. Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. J. Neurosci. 15 (5), 3526–3538.

Dijk, D., Franken, P., 2005. Interaction of sleep homeostasis and circadian rhythmicity: dependent or independent systems. In: Principles and Practice of Sleep Medicine. Elsevier Saunders, Philadelphia, PA, pp. 418–434.

Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315, 629–634.

Ford, D., Kamerow, D., 1989. Epidemiologic study of sleep disturbances and psychiatric disorders. J. Am. Med. Assoc. 262 (11), 1479–1484.

*Gaillard, J.M., Iorio, G., Campajola, P., Kemali, D., 1984. Temporal organization of sleep in schizophrenics and patients with obsessive–compulsive disorder. Adv. Biol. Psychiatry 15, 76–83.

Gangwisch, J.E., Heymsfield, S.B., Boden-Albala, B., et al., 2006. Short sleep duration as a risk factor for hypertension: analyses of the first national health and nutrition examination survey. Hypertension 47 (5), 833–839, http://dx.doi.org/10.1161/01.HYP.0000217362.34748.e0.

[1] Studies included in meta-analysis.

Glickman, G., 2010. Circadian rhythms and sleep in children with autism. Neurosci. Biobehav. Rev. 34 (5), 755–768.
Harvey, A.G., Murray, G., Chandler, R.A., Soehner, A., 2011. Sleep disturbance as transdiagnostic: consideration of neurobiological mechanisms. Clin. Psychol. Rev. 31 (2), 225–235.
Harvey, A.G., 2011. Sleep and circadian functioning: critical mechanisms in the mood disorders? Annu. Rev. Clin. Psychol. 7, 297–319.
Haynes, S.N., Adams, A., Franzen, M., 1981. The effects of presleep stress on sleep-onset insomnia. J. Abnorm. Psychology 90 (6), 601–606.
Higgins, J.P., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. Br. Med. J. 327 (7414), 557–560, http://dx.doi.org/10.1136/bmj.327.7414.557.
*Hohagen, F., Lis, S., Krieger, S., et al., 1994. Sleep EEG of patients with obsessive–compulsive disorder. Eur. Arch. Psychiatry Clin. Neurosci. 243 (5), 273–278.
Huedo-Medina, T.B., Sánchez-Meca, J., Marin-Martinez, F., Botella, J., 2006. Assessing heterogeneity in meta-analysis: Q statistic or I^2 index? Psychol. Methods 11 (2), 193–206.
*Insel, T.R., Gillin, J.C., Moore, A., Mendelson, W.B., Loewenstein, R.J., Murphy, D.L., 1982. The sleep of patients with obsessive–compulsive disorder. Arch. Gen. Psychiatry 39 (12), 1372–1377.
Jones, S.H., 2001. Circadian rhythms, multilevel models of emotion and bipolar disorder—an initial step towards integration? Clin. Psychol. Rev. 21 (8), 1193–1209.
Kajtna, T., Štukovnik, V., Grošelj, L., 2011. Effect of acute sleep deprivation on concentration and mood states with a controlled effect of experienced stress. Zdravniški Vestnik 80 (5), 354–361.
Kenardy, J., Fried, L., Kraemer, H.C., Taylor, C.B., 1992. Psychological precursors of panic attacks. Br. J. Psychiatry 160 (5), 668–673.
*Kluge, M., Schüssler, P., Dresler, M., Yassouridis, A., Steiger, A., 2007. Sleep onset REM periods in obsessive compulsive disorder. Psychiatry Res. 152 (1), 29–35.
Lipsey, M.W., Wilson, D.B., 2001. Practical Meta-Analysis, 49. Sage, Thousand Oaks, CA.
*Mukhopadhyay, S., Fineberg, N.A., Drummond, L.M., et al., 2008. Delayed sleep phase in severe obsessive–compulsive disorder: a systematic case-report survey. CNS Spectr. 13 (5), 406–413.
National Institute of Mental Health, 2013. Arousal and Regulatory Systems: Workshop Proceedings, ⟨http://www.nimh.nih.gov/research-priorities/rdoc/rdoc_arousal_regulatory_systems_workshop.pdf⟩ (updated 2012, accessed December 15, 2013).
Neyeloff, J.L., Fuchs, S.C., Moreira, L.B., 2012. Meta-analyses and forest plots using a Microsoft excel spreadsheet: step-by-step guide focusing on descriptive data analysis. Biomed. Cent. Res. Notes 5 (52), http://dx.doi.org/10.1186/1756-0500-5-52; 10.1186/1756-0500-5-52.
Norton, R., 1970. The effects of acute sleep deprivation on selective attention. Br. J. Psychology 61 (2), 157–161.
Nota, J.A., Coles, M.E., Gibb, B.E., 2014. Obsessions and time of day: a self-monitoring study in individuals with obsessive–compulsive disorder. J. Cogn. Psychother. 28 (2), 1–11.
Ohdo, S., 2007. Chronopharmacology focused on biological clock. Drug Metab. Pharmacokinet. 22 (1), 3–14.
Oral, E., Ozcan, H., Gulec, M., Selvi, Y., Aydin, A., 2011. Psychotropic medications affecting biological rhythm. J. Mood Disord. 1 (4), 169–177.
Paterson, J.L., Reynolds, A.C., Ferguson, S.A., Dawson, D., 2013. Sleep and obsessive–compulsive disorder (OCD). Sleep Med. Rev. 17 (6), 465–474.
Perlis, M.L., Giles, D.E., Buysse, D., Tu, X., 1997. Self-reported sleep disturbance as a prodromal symptom in recurrent depression. J. Affect. Disord. 42 (2), 209–212.
*Ramsawh, H.J., Stein, M.B., Belik, S., Jacobi, F., Sareen, J., 2009. Relationship of anxiety disorders, sleep quality, and functional impairment in a community sample. J. Psychiatr. Res. 43 (10), 926–933.
*Robinson, D., Walsleben, J., Pollack, S., Lerner, G., 1998. Nocturnal polysomnography in obsessive–compulsive disorder. Psychiatry Res. 80 (3), 257–263.
Schubert, J.R., Coles, M.E., 2013. Obsessive–compulsive symptoms and characteristics in individuals with delayed sleep phase disorder. J. Nerv. Ment. Dis. 201 (10), 877–884, http://dx.doi.org/10.1097/NMD.0b013e3182a5eb13; 10.1097/NMD.0b013e3182a5eb13.
Schwartz, J.R., Roth, T., 2008. Neurophysiology of sleep and wakefulness: basic science and clinical implications. Curr. Neuropharmacol. 6 (4), 367–378, http://dx.doi.org/10.2174/157015908787386050; 10.2174/157015908787386050.
Spiegel, R., 1981. Sleep and Sleeplessness in Advanced Age: Advances in Sleep Research. MTP Press, Lancaster, UK.
Takano, K., Tanno, Y., 2011. Diurnal variation in rumination. Emotion 11 (5), 1046–1058.
Tang, N.K.Y., Harvey, A.G., 2004. Effects of cognitive arousal and physiological arousal on sleep perception. Sleep 27 (1), 69–78.
Thomsen, D.K., Yung Mehlsen, M., Christensen, S., Zachariae, R., 2003. Rumination—relationship with negative mood and sleep quality. Pers. Indiv. Differ. 34 (7), 1293–1301.
Tsuno, N., Besset, A., Ritchie, K., 2005. Sleep and depression. J. Clin. Psychiatry 66 (10), 1254–1269.
*Turner, J., Drummond, L.M., Mukhopadhyay, S., et al., 2007. A prospective study of delayed sleep phase syndrome in patients with severe resistant obsessive–compulsive disorder. World Psychiatry 6, 108–111.
van der Helm, E., Walker, M.P., 2009. Overnight therapy? The role of sleep in emotional brain processing. Psychol. Bull. 135 (5), 731–748.
van der Helm, E., Walker, M.P., 2012. Sleep and affective brain regulation. Soc. Pers. Psychol. Compass 6 (11), 773–791.
*Voderholzer, U., Riemann, D., Huwig-Poppe, C., et al., 2007. Sleep in obsessive compulsive disorder. Eur. Arch. Psychiatry Clin. Neurosci. 257 (3), 173–182.
*Walsleben, J., Robinson, D., Lemus, C., Hackshaw, R., Norman, R., Alvir, J., 1990. Polysomnographic aspects of obsessive–compulsive disorders. Sleep Res. 19, 177.
Weitzman, E.D., Czeisler, C.A., Coleman, R.M., et al., 1981. Delayed sleep phase syndrome: a chronobiological disorder with sleep-onset insomnia. Arch. Gen. Psychiatry 38, 737–746.
World Health Organisation, 1979. International Statistical Classification of Disease, ninth ed. Author, Geneva, Switzerland.
Wright Jr., K.P., Hull, J.T., Hughes, R.J., Ronda, J.M., Czeisler, C.A., 2006. Sleep and wakefulness out of phase with internal biological time impairs learning in humans. J. Cogn. Neurosci. 18 (4), 508–521.
Wulff, K., Gatti, S., Wettstein, J.G., Foster, R.G., 2010. Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. Nat. Rev. Neurosci. 11 (8), 589–599.